Applicants have amended claims 1, 2, 3 and 5 and such amendments raise no issue of new matter. Support for the amendment to claim 1 may be found on page 22, lines 20-24. Support for "neuronal" in claim 2 may be found on page 12, line 11. Support for the amendment to claim 5 may be found on page 11, lines 9-10.

The amendments to the specification are fully supported. Applicants point out that Tables 1 and 2 (on substitute pages 24 and 25 attached hereto as **Exhibit A**) are identical to Tables 1 and 2 of Hardy, J. Amyloid, The Presenilins and Alzheimer's disease, Trends Neurosci. 20: 154-159 (1997) which document was incorporated by reference into the subject application. Applicants have now included Tables 1 and 2 of this document into the subject application. Applicants maintain that this amendment raises no issue of new matter. In addition, Table 3 (on substitute page 26 attached hereto as **Exhibit A**) is identical to Table 1 of Tanzi, R., Kovacs, D., Kim, T., Moir, R., Guenette, S., Wasco, W. The gene Defects Responsible For Familial Alzheimer's Disease, Neurobiol. Dis. 3: 159-168 (1996) which document was also incorporated by reference into the subject application. Applicants maintain that this amendment raises no issue of new matter. Therefore, applicants request that the Examiner enter this amendment.

Election/Restriction

The Examiner entered applicants' election, with traverse, of Group I, claims 1-5, 11, and 12, in reply to the restriction requirement.

The Examiner stated that while the invention involves compounds which inhibit neurotoxicity, the claims are not drawn to the compounds *per se*. The Examiner stated that using the example provided by applicants, the invention is directed to methods of screening and cells which have been modified by introduction of

recombinant DNA into the cells. The Examiner stated that the claims of Group I are directed to a method for evaluating the ability of a compound to inhibit neurotoxicity which requires cells containing RAGE and a mutant presenilin-2 protein, and a step of measuring cell death. The Examiner stated that the claims of Group II, directed to a method for evaluating the ability of a compound to inhibit binding of amyloid β peptide to a receptor, requires cells containing RAGE and a mutant presenilin-2, and a step of measuring receptor-ligand binding activity. The Examiner stated that while the methods required the same cell, the measurements used for evaluating the compounds which are added to the cells are distinct. The Examiner stated that moreover, since the measurement step required in the method of Group I, determination of cell death, is not required to reduce to practice the method of Group II, and the measurement step of Group II, determination of receptor-ligand binding, is not required to reduce to practice the method of Group I, the method are also distinct.

The Examiner stated that with regard to cells required for the methods of Groups I and II, and the claimed cells of Group V, it should be noted that the cells of Groups I and II are not required to be modified using recombinant DNA technology as these cells can be obtained from naturally occurring sources. The Examiner stated that the cells of Group V, however, require introduction of foreign DNA for expression of the mutant protein. The Examiner stated that thus, the sources of the cells and/or the methods of obtaining the cells are distinct as they require different technical considerations. The Examiner stated that moreover, the recombinant cells of Group V are not required to reduce to practice the methods of Group I and II, nor are the methods of Groups I and II required to reduce to practice the composition of Group V. The Examiner maintained the restriction requirement.

Objection to Abstract of the Disclosure

The Examiner objected to the Abstract of the Disclosure because it contains multiple paragraphs and exceeds 250 words in length.

In reply, applicants have amended the Abstract of the Disclosure and request that the Examiner withdraw this ground of objection.

Rejection Under 35 U.S.C. §112, 2nd paragraph

The Examiner rejected claims 1-5, 11 and 12 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claim 1 is rendered vague and indefinite by the phrase "mutant presenilin-2 protein" because it is unclear what type of mutation is required in the protein for the cell to be suitable in the claimed method.

The Examiner stated that claim 2 is rendered vague and indefinite by the phrase "tumor cell" because it is unclear which type of tumor is suitable in the claimed method.

The Examiner stated that claim 3 is rendered vague and indefinite by the term "polymer" as it is unclear what type of polymer is encompassed in the claim, e.g., is the polymer a synthetic polymer, a naturally occurring polymer, a nucleic acid polymer, a carbohydrate polymer?

The Examiner stated that claim 3 is further rendered vague and indefinite by the phrase "small molecule" because it is unclear what Applicants intend as "small", i.e., does the term small denote

a weight limitation of a spatial limitation on the molecule?

The Examiner stated that claim 5 is rendered vague and indefinite by the phrase "mutant presenilin-2 is overexpressed" because it is unclear if the overexpression occurs at the transcriptional or translational level. The Examiner stated that the phrase as written, lacks proper antecedent basis. The Examiner stated that applicants should insert the therm "protein" after "mutant presenilin-2".

In reply, applicants respectfully traverse the rejection. Applicants have amended claims 1, 2, 3 and 5 to more particularly point out the presently claimed invention. As to the Examiner's concerns regarding claim 1, applicants maintain that "mutant presenilin-2 protein" is clearly described in the specification on page 11, lines 11-15 and on page 22, lines 20-24. An example of a mutant presenilin-2 protein is referred to in Wolozin et al. 1996 and is designated N141 mutant, see page 24, lines 5-10 of the subject application. In addition, applicants have amended claim 1 to recite that the mutant presenilin-2 protein be capable of causing increased basal apoptosis in nerve growth factor-differentiated PC12 cells.

As to claim 2, applicants have amended the claim to recite "neuronal tumor cell" in the interest of accelerated prosecution and maintain that any tumor cell would be useful in the claimed invention. Applicants do not concede to the correctness of the Examiner's statements.

As to claim 3, applicants maintain that any polymer and any small molecule can be employed in the practice of the claimed invention. However, without conceding the correctness of the Examiner's statements and to accelerate prosecution of the application,

applicants have amended claim 3.

As to claim 5, applicants maintain that the Examiner's query regarding whether "overexpression occurs at the transcriptional or translational level" is irrelevant to the presently claimed invention. The claim is directed to overexpression of the protein and it is irrelevant whether the mechanism of overexpression is at the transcriptional or translational level. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In view of the above remarks and amendments, applicants request that the Examiner reconsider and withdraw these various rejections under 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §112, 1st paragraph

The Examiner rejected claims 1-5, 11 and 12 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is the Examiner's position that the method requires a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein. The Examiner stated that however, the specification fails to provide an enabling disclosure as to the public availability of the cell, a mutant presenilin-2 protein, or how to make the cell such that the mutant presenilin-2 protein is expressed.

The Examiner stated that the specification teaches numerous cell types which can be used in the method, but does not disclose if the

cells contain a naturally-occurring mutation on the presenilin-2 protein, or whether genetic modification of the cell types is required. The Examiner stated that with regard to the type of mutation, the specification teaches that the mutant protein may be a result of a deletion, substitution, insertion, or point mutation. The Examiner stated that moreover, the protein can be of human or non-human origin, and can be overexpressed. The Examiner stated that however, the specification fails to proved an enabling disclosure for how to make generate these various mutations as there is no teaching as to specific presenilin-2 sequences and/or restriction maps to generate constructs for transfection of the cells such that they express or over-express the mutant presenilin-2 protein.

The Examiner stated that while the specification discloses, by reference to a printed publication, that PC12 cells are transfected with a mutant presenilin-2 construct, the specification does not disclose how to make the construct for transfecting the cells. The Examiner stated that the attempt to incorporate subject matter into this application by reference to Wolozin (1996) is improper because a cell containing the mutant presenilin-2 protein is a critical feature of the invention.

The Examiner stated that the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. The Examiner stated that applicant is required to amend the disclosure to include the material incorporated by reference. The Examiner stated that the amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consist of the same material incorporated by reference in the referencing application.

The Examiner stated that in view of the non-enabling disclosure for making a cell which expresses or over-expresses a mutant presenilin-2 protein, the method of using the cell, and the product identified by the method are also not enabled.

In reply, applicants respectfully traverse the rejection and maintain that the claimed invention is fully enabled.

Applicants' claimed invention is a method for evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein in a cell culture and the compound, wherein the mutant presenilin-2 protein is capable of causing increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) determining the level of cell death in the cell culture; and c) comparing the level of cell death determined in step (b) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity.

Applicants have amended the specification to include examples of specific presenilin-2 protein mutations (in Tables 1-3) which were included in publications which the subject application incorporated by reference. By this amendment, applicants have included the examples of mutant presenilin-2 proteins in the specification. Applicants maintain that one of ordinary skill in the art would have a reasonable likelihood of success in carrying out the claimed invention in view of the disclosure of the subject application. Applicants submit that making a cell which expresses or overexpresses a mutant presenilin-2 protein is fully enabled. Tables 1-3 on substitute pages 24-26 indicate specific base pair changes to the known sequence of human presenilin-2 which would result in mutants as recited in claim 1. Applicants maintain that

the transfection of PC12 cells is a routine technique that would have been well known to one of ordinary skill in the art. In view of these amendments and remarks, applicants submit that the claimed invention is fully enabled and described in the subject specification. Thus, applicants respectfully request the Examiner to withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 1-5, 11 and 12 under 35 U.S.C. §102 (b) as being anticipated by Bartus et al. (U.S. Patent No. 5,444,042, 1995).

The Examiner stated that Bartus et al. disclose that calpain activation is an event central to many cases of brain atrophy and degeneration and that inhibition of calpain alone if sufficient to inhibit or prevent cell deterioration and loss (see column 6, lines 16-23). The Examiner stated that Bartus et al. teach a method of evaluating the ability of a compound to inhibit neurotoxicity comprising treating N18-RE-105 cells with calpain inhibitors and measuring the extent of cell death. The Examiner stated that the calpain inhibitors effectively block cell death in an *in vitro* model for neuropathology (see column 73, lines 5-24). The Examiner stated that the compounds can be formulated as pharmaceutical compositions comprising the compound of interest in a pharmaceutically acceptable formulation containing a carrier material (see column 4, lines 48-54 and column 66, lines 36-40).

In reply, applicants traverse the rejection. Applicants' claimed invention is directed to a method for evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein in a cell culture

and the compound, wherein the mutant presenilin-2 protein is capable of causing increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) determining the level of cell death in the cell culture; and c) comparing the level of cell death determined in step (b) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity.

Applicants submit that Bartus et al. do not anticipate the claimed invention. Specifically, Bartus et al. do not teach a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein. Specifically, N18-RE-105 cells are not cells which express a mutant presenilin-2 protein as required by the claimed invention. A reference must teach all of the features recited in the claimed invention in order to anticipate a claimed invention under 35 U.S.C. §102. Applicants submit that Bartus et al. do not teach all of the features of the claimed invention and therefore, respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 1-5, 11, and 12 under 35 U.S.C. §103(a) as being unpatentable over Bartus et al.

The Examiner stated that Bartus et al. disclose that calpain activation is an event central to many cases of brain atrophy and degeneration and that inhibition of calpain alone is sufficient to inhibit or prevent cell deterioration and loss (see column 6, lines 16-23). The Examiner stated that Bartus et al. teach a method of evaluating the ability of compound to inhibit neurotoxicity comprising treating N18-RE-105 cells with calpain inhibitors and measuring the extent of cell death. The Examiner stated that the

calpan inhibitors effectively block cell death in an in vitro model for neuropathology (see column 73, lines 5-24).

The Examiner stated that Bartus et al. do not disclose all of the claim-designated compounds recited in claim 3. The Examiner stated that however, as the method of evaluating compounds is known in the art, it would have been obvious and well within the purview of one ordinary skill in the art to substitute classes of compounds in various formulation in the method of evaluating the effect of these compounds of cell death absent evidence to the contrary.

In reply, applicants vigorously traverse the rejection. Bartus et al. do not suggest or make obvious the use of a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein as presently claimed. Specifically, Bartus et al. do not render obvious a method for evaluating the ability of a compound to inhibit neurotoxicity which comprises: (a) contacting a cell which expresses a receptor for advanced glycation end product protein and a mutant presenilin-2 protein in a cell culture and the compound, wherein the mutant presenilin-2 protein is capable of causing increased basal apoptosis in nerve growth factor-differentiated PC12 cells; (b) determining the level of cell death in the cell culture; and c) comparing the level of cell death determined in step (b) with the amount determined in the absence of the compound so as to evaluate the ability of the compound to inhibit neurotoxicity.

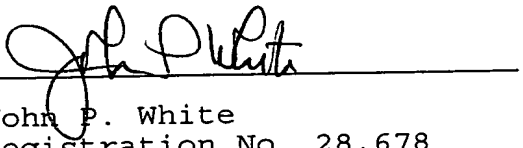
Bartus et al. teach a method of treatment of neurodegeneration with calpain inhibitors. Example 5 of Bartus et al., upon which the Examiner relies, merely indicates that stock cultures of N18-RE-105 were treated with various concentrations of calpain inhibitors. This does not make obvious contacting a cell which expresses a mutant presenilin-2 protein with a compound in order to evaluate

the compound's ability to inhibit neurotoxicity. Furthermore, Example 5 at column 73 is entitled "Inhibition of Glutamate-Induced Cell Death" which is a different type of cell death than recited in the claimed invention. As recited in claim 1, the presenilin-2 mutant protein is characterized in that it is capable of causing increased basal apoptosis in nerve growth factor-differentiated PC12 cells. Bartus et al. do not render obvious the claimed invention. One of ordinary skill in the art would have no liklihood of success, indeed would have no hint of the claimed invention, in view of Bartus et al. Thus, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other than the $435.00 three-month extension of time fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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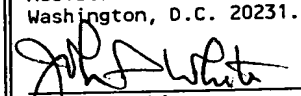

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